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Scientific Integrity Official
Office of Research and Development
U.S. Environmental Protection Agency
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Washington, DC 20460

Re: Objectivity and transparency concerns in the Integrated Risk Information System – September 2011 Toxicological Review of Trichloroethylene

Dear Dr. Grifo:

The American Chemistry Council (ACC) has been actively engaged in the National Center for Environmental Assessment's (NCEA) Integrated Risk Information System (IRIS) for many years and has closely followed NCEA's efforts to implement the 2011 and 2014 recommendations of the National Research Council (NRC) to improve the IRIS assessment process. Although NCEA has made progress in addressing the NRC recommendations, the IRIS process continues to suffer from the absence of a clearly defined and transparent process for systematically reviewing the data available for a chemical.

Incorporating systematic review[1] throughout a chemical evaluation, but particularly in the data-review step, provides a framework to document and support the decisions made. It allows for greater transparency in the source of the data considered, the methods of quality assessment used, and the scientific judgments made during evidence integration.[2] As such, the use of systematic review of data in the IRIS assessment program is essential to ensuring the objectivity, clarity, reproducibility, and utility of IRIS assessments, as well as the many Agency programs that depend on the information contained within the assessments.

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[1] According to the National Academy of Sciences' Institute of Medicine (IOM) systematic review "is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. (IOM. Finding what works in health care: standards for systematic reviews. National Academies Press, Washington, DC. 2011). Systematic review methodologies are well established in medicine, but have been a more recent development in the field of chemical risk assessment.

[2] Rooney AA *et al.* Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspec* 122(7):711-718 (2014).

In light of your efforts to engage external parties in ensuring the highest level of scientific integrity at EPA and to develop best practices for the clearance of the Agency's scientific content, ACC would like to call your attention to this critical issue. This letter discusses why ensuring that the IRIS program incorporates systematic review into its assessments should be of significant interest to the Scientific Integrity Committee. We also review NCEA's consideration of trichloroethylene (TCE) as recent evidence of the problems with the current approach, and request that the Scientific Integrity Committee recommend that NCEA take immediate action to address these important shortcomings, particularly in relation to TCE.

Concern about the lack of a well-defined process for selecting and evaluating studies used in IRIS has been voiced by reviewers for nearly a decade. In its 2011 review of the draft assessment for formaldehyde, the NRC noted that –

> [t]he general problems that the committee identified are not unique to the draft IRIS assessment of formaldehyde. Committees of the Board on Environmental Studies and Toxicology (BEST) of the [NRC] have reviewed a number of IRIS assessments in the last decade, including three . . . in the last 5 years. Some of the general problems identified by the present committee have been commented on by the other BEST committees. For example, the 2006 NRC report on dioxin and related compounds commented on the need for formal, evidence-based approaches for noncancer effects, the need for transparency and clarity in the selection of data sets for analysis, and the need for greater attention to uncertainty and variability. . . The 2010 NRC review of the draft IRIS assessment of tetrachloroethylene found similar problems and provided a chapter, "Moving Beyond the Current State of Practice," that addressed methodologic issues and the failure to establish clear and transparent methods for carrying out and presenting the assessment . . . That report also provided a broad set of recommendations on characterization of uncertainty.[3]

The 2011 NRC report (NRC 2011) noted that applying standard study quality criteria would improve the transparency and consistency of IRIS assessments.[4] The report added that the evaluation and selection of available studies "is related to a fundamental issue of filtering the literature to identify the studies that provide the best dose-response information."[5]

In its subsequent 2014 review of the IRIS program (NRC 2014), NRC observed that "although EPA has identified and is assessing important characteristics of the quality of human and animal

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3 NRC. A review of the Environmental Protection Agency's draft IRIS assessment of formaldehyde. National Academies Press, Washington, DC (2011), at 24.

4 Segal D *et al.* Evaluation of the ToxRTool's ability to rate the reliability of toxicological data for human health hazard assessments. *Reg Toxicol Pharma* 72(1):94-101 (2015).

5 NRC 2011, at 160.

studies, it has not historically conducted the assessments in a consistent and standardized way for studies included in IRIS assessments."[6] NRC 2014 concluded that -

> experience gained from randomized clinical trials in human and veterinary medicine suggests that systematic reviews that assess animal toxicology studies for quality and risk of bias[7] would improve the quality of IRIS reviews.[8]

The report further explained that "there is no assessment of the risk of bias in the studies evaluated" in IRIS assessments, nor do they include a "description of quality-assurance measures for the collection of assessment data."[9]

Earlier this year, EPA's own Science Advisory Board (SAB) commented on the lack of a standardized and systematic approach to evaluating studies as part of the draft IRIS assessments for ammonia, ethylene oxide, and trimethylbenzenes.[10] In its review of the assessment for ammonia, the Board's draft letter notes -

> Although the narrative provides an evaluation of the studies according to preselected criteria, not all criteria recommended by the NRC (2011) are incorporated (e.g., precision of the effect) and there is no specific overall study quality indicator. While it is understood that this is an area still under development, the application of the study quality criteria for the selection and evaluation of key non-cancer experimental animal studies that were included in the assessment is unclear.[11]

In failing to incorporate a systematic review of study quality in its IRIS assessments, NCEA is falling behind its counterparts within the federal government – including the National Toxicology Program[12] and EPA's Office of Pesticide Programs[13] – and elsewhere in the world who have recognized that systematic review "has the potential to increase objectivity and transparency much

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6 NRC. Review of EPA's Integrated Risk Information System (IRIS) process. National Academies Press, Washington, DC (2014), at 66.

7 An assessment of study quality evaluates the extent to which the researchers conducted their research to the highest possible standards and how a study is reported. Risk of bias is related to the internal validity of a study and reflects study-design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect. (NRC 2014, at 7)

8 NRC 2014, at 71.

9 Ibid, at 65.

10 Draft letters on the three assessments are available on the web site summarizing the SAB's June 8 meeting.

11 SAB Review of the draft toxicological profile for ammonia (May 1, 2015), at 10.

12 http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html.

13 http://www.epa.gov/pesticides/science/lit-studies.pdf

like it has already done for clinical medicine."[14] As part of its implementation of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, the European Chemicals Agency (ECHA) calls for the thorough evaluation of all data, at the start of the chemical registration process, to determine if they are reliable and sufficient for use in regulatory decisions.[15] The European Food Safety Authority (EFSA) also has incorporated systematic review methodologies into their safety assessments to support decision making.[16]

Establishment of a transparent, reproducible, and scientifically defensible process for evaluating individual studies is long overdue within the IRIS program. As noted by the NRC -

> an IRIS assessment needs to include a transparent evaluation of the risk of bias of studies used by EPA as a primary source of data for the hazard assessment. EPA should specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream. [17]

NRC further recommended that "[t]he plan for incorporating the risk-of-bias assessment into a systematic review should be specified a priori in the review protocol."[18]

I have enclosed a recent critique of NCEA's evaluation of non-cancer endpoints for TCE as part of its 2011 IRIS assessment for the substance to illustrate the problems that still exist in the IRIS assessment process. As explained in the critique, NCEA focuses on three unreliable studies to develop its reference values for TCE and, in lieu of a systematic process for evaluating these studies, offers only subjective justification for their use.[19] Despite the concerns that have been raised by numerous reviewers about NCEA's study selection, particularly about data on fetal heart effects in animals reported by a single laboratory, the reference values from the 2011 assessment are being used by EPA's Office of Chemical Safety and Pollution Prevention (OCSPP)[20] and Office of Solid

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14 Rooney *et al.* 2014.

15 ECHA. Guidance on information requirements and chemical safety assessment. Chapter R.4: Evaluation of available information. Guidance for the implementation of REACH (May 2008).

16 EFSA. Application of systematic review methodology to food and feed safety assessments to support decision making. *EFSA Journal* 8(6):1637 (2010).

17 NRC 2014, at 79.

18 Ibid, at 76.

19 ACC's critique applies the reliability criteria identified by Klimisch *et al.* (1997) that form the basis for data evaluations conducted under REACH. Although the Klimisch approach may not eliminate the need for subjective evaluation, it can provide EPA with a more consistent method for data evaluation. (See Segal *et al.* 2015.)

20 EPA. TSCA work plan chemical risk assessment - trichloroethylene: degreasing, spot cleaning and arts & crafts uses. Office of Chemical Safety and Pollution Prevention. EPA-Document # 740-R1-4002 (June 2014).

Waste and Emergency Response (OSWER).[21] In addition, the Agency for Toxic Substances and Disease Registry (ATSDR) has proposed to adopt the IRIS values in updating its Toxicological Profile for TCE.[22]

The controversy surrounding EPA's dependence on flawed study data in their assessment of non-cancer effects of TCE is underscored by a 2014 update of the fetal heart toxicity assessment conducted by EPA staff that appeared in the OCSPP docket.[23] While this update was neither a systematic,[24] nor an independent,[25] review of the available cardiac data, it notes that seven of the 11 members of the update team characterized the confidence in the dose-response evaluation of the cardiac data as "low," and the other four members characterized it as "low to medium." These views differ significantly from that of the 2011 assessment; yet the IRIS summary for TCE has not been updated to reflect the lower confidence ratings of this subsequent review. Nor has the IRIS Summary or the IRIS Toxicological Profile for TCE been annotated to make users aware of this more recent internal review.

NCEA's failure to address the repeated recommendations from the NRC to implement a systematic review process for assessing individual studies that are selected for inclusion in its reviews threatens the objectivity, clarity, reproducibility, and utility of IRIS, as well as the many EPA programs that depend on it. Although NCEA has expressed its intent to incorporate systematic review in the IRIS process as part of a "handbook" for developing IRIS assessments, the effort is moving far too slowly.[26] In the meantime, the IRIS program continues to develop assessments, like the one developed for TCE, that lack the quality and transparency that a systematic review process would provide.

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21 See Vapor Intrusion Screening Level calculator (VISL) available at http://epa.gov/oswer/vaporintrusion/guidance.html.

22 ATSDR. Draft Toxicological Profile for Trichloroethylene (October 2014).

23 TCE developmental cardiac toxicity assessment update (undated). (Document ID EPA-HQ-OPPT-2012-0723-0045 available at http://www.regulations.gov) The update was added to the docket in July 2014 shortly before a public workshop on TCE and does not appear to have been announced publicly. Although the summary table from the update was included as an appendix to the final TSCA work plan chemical risk assessment for TCE, existence of the full document only came to light by way of a footnote in a response to an Information Quality Guidelines request issued earlier this year.

24 The conclusions of the 2014 review focus on the methodologies used to derive a point of departure from the data, rather than on the study quality and the risk of bias.

25 The review team responsible for the update included several authors of the 2011 IRIS assessment, including both the chemical manager for the IRIS review and the lead for the 2014 update.

26 Portions of the IRIS handbook were provided to the NRC as part of its 2014 review, but a complete version of the document has not been made available.

In light of the controversy surrounding NCEA's derivation of reference values for TCE,[27] and the impact that those values have had, and will have, on decisions made by OCSPP, OSWER, ATSDR and elsewhere, we respectfully request that the Scientific Integrity Committee ensure that NCEA prioritize the reassessment of the reference values for TCE in the IRIS assessment. This analysis should be conducted under a process for systematic review, as described above, that has been subject to external peer review. Moreover, until the science is appropriately evaluated, we ask that the Science Integrity Committee request that the reference values for TCE be withdrawn from the IRIS summary for TCE included on EPA's website or, at the very least, that the website indicate that the values are under review. These changes are necessary to ensure that the IRIS reference values are not inappropriately used to inform important regulatory policy decisions at state or federal levels.

I look forward to discussing this issue with you and/or the Committee. I will contact you in the near future to arrange a meeting. In the meantime, please feel free to contact me at (202) 249-6727 or at srisotto@americanchemistry.com if you have questions about the above information.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

Enclosure

cc: T. Burke, Science Advisor and Deputy AA for Research and Development
L. Kadeli, Acting AA for Research and Development
K. Olden, Director, NCEA
V. Cogliano, Director, IRIS Division

[27] In addition to the issues outlined in this letter, a recent submission to EPA's Information Quality Guidelines office suggests that one of the participants in the SAB's review of the draft IRIS assessment had a clear conflict of interest.